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Tumor-Induced Osteomalacia and Symptomatic Looser Zones Secondary to Mesenchymal Chondrosarcoma

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Tumor-induced osteomalacia is a rare clinical entity that is associated with soft-tissue or skeletal tumors. We present a case report of a patient with a chest wall mesenchymal chondrosarcoma who presented with bone pain. The patient had skeletal changes in the femoral neck and fibula consistent with osteomalacia and laboratory values suggesting phosphate diabetes. The patient was treated with tumor resection and phosphate supplementation with reversal of the signs and symptoms of osteomalacia. Tumor-induced osteomalacia is vitamin-D–resistant and often reversed by complete removal of the tumor. Most commonly, the causative tumors are of vascular, mesenchymal, or fibrous origin. The osteomalacia is associated with bone pain, muscle weakness, and radiographic changes. Tumor-induced humoral factors have been implicated in causing the osteomalacia, but the definite etiology has yet to be determined. Current treatment includes complete tumor resection and electrolyte supplementation.
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KEY WORDS: **phosphate diabetes; oncogenic osteomalacia; chondrosarcoma**

INTRODUCTION

Tumor-induced osteomalacia is a rare clinical entity associated with either skeletal or soft-tissue tumors. The osteomalacia is vitamin-D–resistant and is often reversed by complete removal of the tumor. We present a report of a man with a 16-year history of a chest wall mass later diagnosed as mesenchymal chondrosarcoma who presented with bone pain and skeletal changes consistent with osteomalacia.

CASE REPORT

The patient is a 46-year-old white male who was incidentally noted to have a small soft-tissue lesion over his right rib cage after a motor vehicle accident in 1977. He refused a recommended excisional biopsy at that time. Although he noted gradual growth of the mass, he did not seek follow-up until 1991 when he developed right groin and leg pain with bilateral heel pain. Additionally, the patient developed muscular weakness (unable to rise from a squat or lift objects), nocturia, and diffuse bone pain. On physical examination, the soft-tissue mass on his right flank was noted to have enlarged to approximately 20 × 28 cm and involved the 10th through 12th ribs. Plain films demonstrated apparent insufficiency fractures of his right fibula and right femoral neck (Fig. 1). The femoral lesion was initially diagnosed as a stress fracture and surgical fixation was advised by an outside physician. The patient, however, refused operative fixation. The horizontal orientation of the fibula fracture as well as the compression-side cortical defect in the medial femoral neck were characteristic of Looser zones seen in osteomalacia. Looser zones (or lines) have been described radiographically as ribbon-like bands of radiolucency that are directed into the bones at approxi-

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Fig. 1. Looser zones are demonstrated in the medial femoral neck and fibula consistent with the patient's symptoms of pain and diagnosis of osteomalacia.

mately right angles to the margins [1]. Also noted radiographically was lack of differentiation between the cortex and the medullary canal suggesting diffuse osteopenia consistent with osteomalacia. Stress fractures are more commonly encountered on the tension side of bones, and the radiographic response is often osteoblastic, thereby distinguishing these lesions from Looser lines. Resection of the thoracic wall lesion was again advised, and the patient agreed to operation. Preoperative total-body bone scan and chest computed tomography (CT) were obtained to further evaluate the lesion and possible metastasis (Figs. 2 and 3). Multiple sites of scintigraphic uptake were demonstrated in the ribs, in addition to the previously identified skeletal lesions.

Preoperative laboratory values revealed a consistently low serum phosphorus level ranging from 1.0 mg/dl to 2.2 mg/dl (normal reference levels 2.4–4.5 mg/dl). Alkaline phosphatase was elevated at 147 U/L (normal reference levels 35–135 U/L). He had normal serum levels of 25 hydroxy vitamin-D: 41 pg/ml (normal reference levels 15–60 pg/ml); parathyroid hormone intact: 63.8 pg/ml (normal reference levels 10–65 pg/ml); calcium: 8.9 mg/dl (normal reference levels 8.5–10.5 mg/dl); and magnesium: 2.2 mg/dl (normal reference levels 1.8–2.8 mg/dl). Serum total protein and albumin were also within normal limits. A 24-hr total urine phosphorus revealed probable impairment of renal tubular reabsorption of phosphate. These values suggest renal phosphate wasting (phosphate diabetes) as the probable cause for the apparent oncogenic osteomalacia.

On 17 November 1993, the patient was taken to the operating room for tumor resection. The tumor was found to involve portions of the 10th, 11th, and 12th ribs as well as the pleura and right hemidiaphragm. The 14.3 × 14.2 × 10.4 cm tumor (Fig. 4) was successfully resected by a combined surgical team of general and plastic surgeons, and coverage was obtained using prolene mesh and a latissimus dorsi regional muscle flap. The patient tolerated surgery well, and his postoperative course was hindered only by a transient coagulopathy.

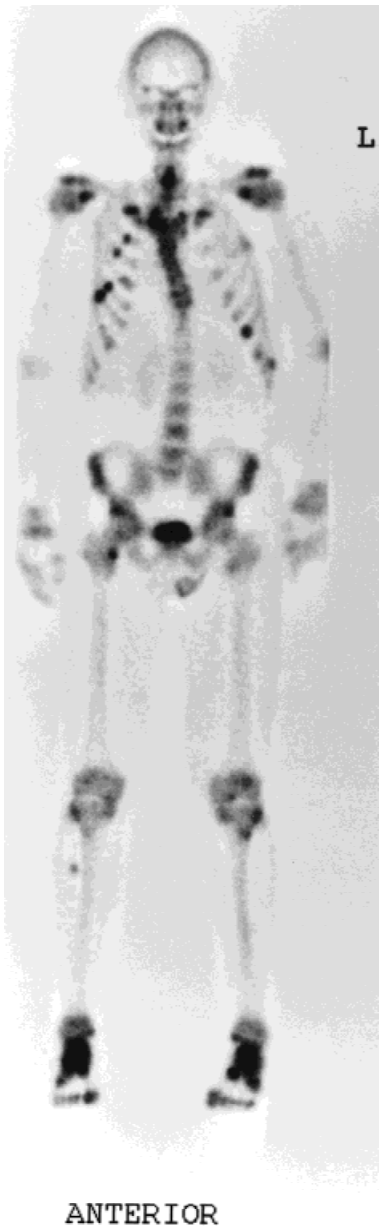

Fig. 2. Total body bone scan demonstrating increased radioisotope uptake in numerous ribs as well as the right hip and fibula.

Pathologic examination of the mass revealed a mesenchymal chondrosarcoma with the surgical margins free of tumor. Mesenchymal chondrosarcoma is a variant of chondrosarcoma characterized by a dimorphic histologic pattern with abrupt changes between well-differentiated cartilage and poorly differentiated small cells. The small cells rarely demonstrate pleomorphism or mitotic figures

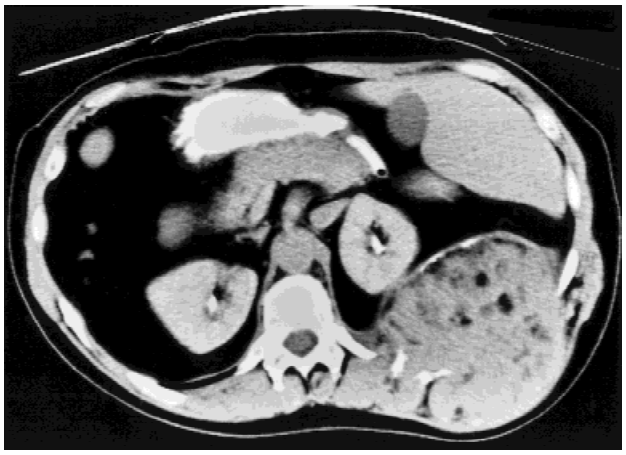

Fig. 3. Axial computerized tomography of the chest demonstrating the chest wall lesion involving ribs and protruding into the chest cavity.

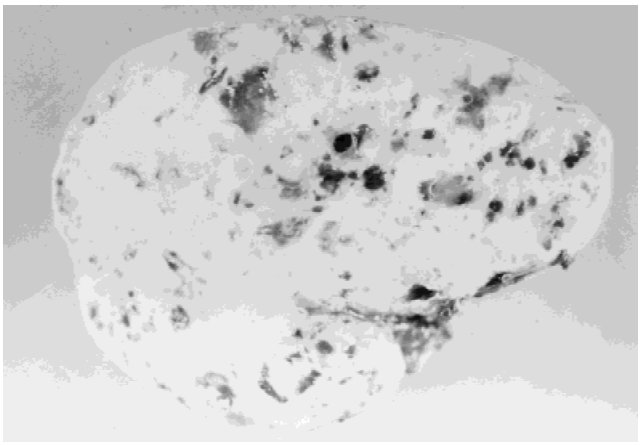

Fig. 4. Photograph of surgical specimen demonstrating mass, which was red-brown and gray, measuring 14.3 × 14.2 × 10.4 cm.

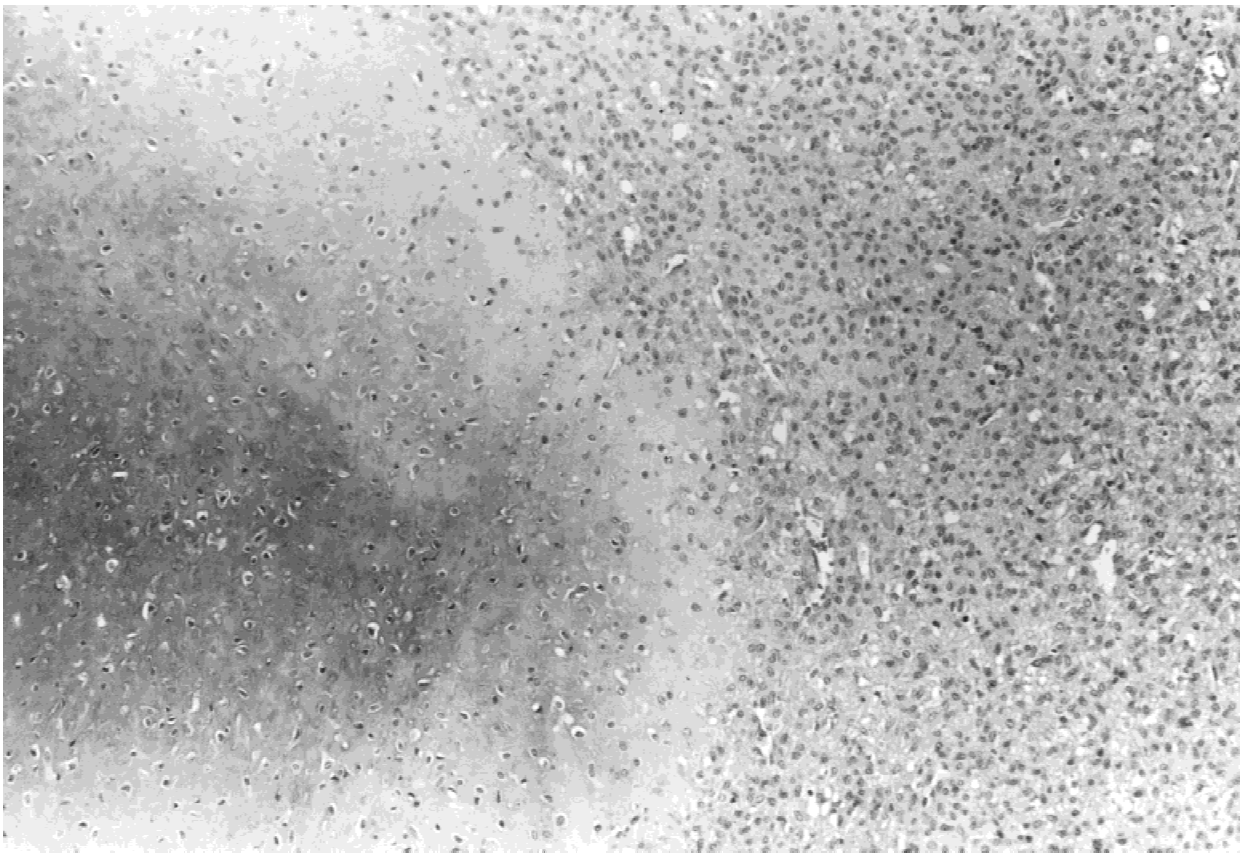

Fig. 5. At low power (magnification: 40×), the dimorphic pattern of the tumor is demonstrated by the abrupt boundary between the area of well-differentiated tumor showing hypocellular cartilagenous matrix and the hypercellular undifferentiated small cell component.

(Figs. 5 and 6) [2]. No pathologic confirmation of osteomalacia was available.

The patient was treated with supplemental oral phosphate and his serum values on postoperative day 4 were phosphorus, 3.3 mg/dl; calcium, 7.8 mg/dl; and 25 hydroxy vitamin-D, 159 pg/ml. The patient was placed on protected weight-bearing as tolerated with crutches for treatment of his insufficiency fractures. His symptoms diminished, and radiographs demonstrated progressive healing of the previously noted insufficiency fractures at 1-month follow-up. Concurrently, his serum calcium, magnesium, and phosphorus levels normalized. Com-

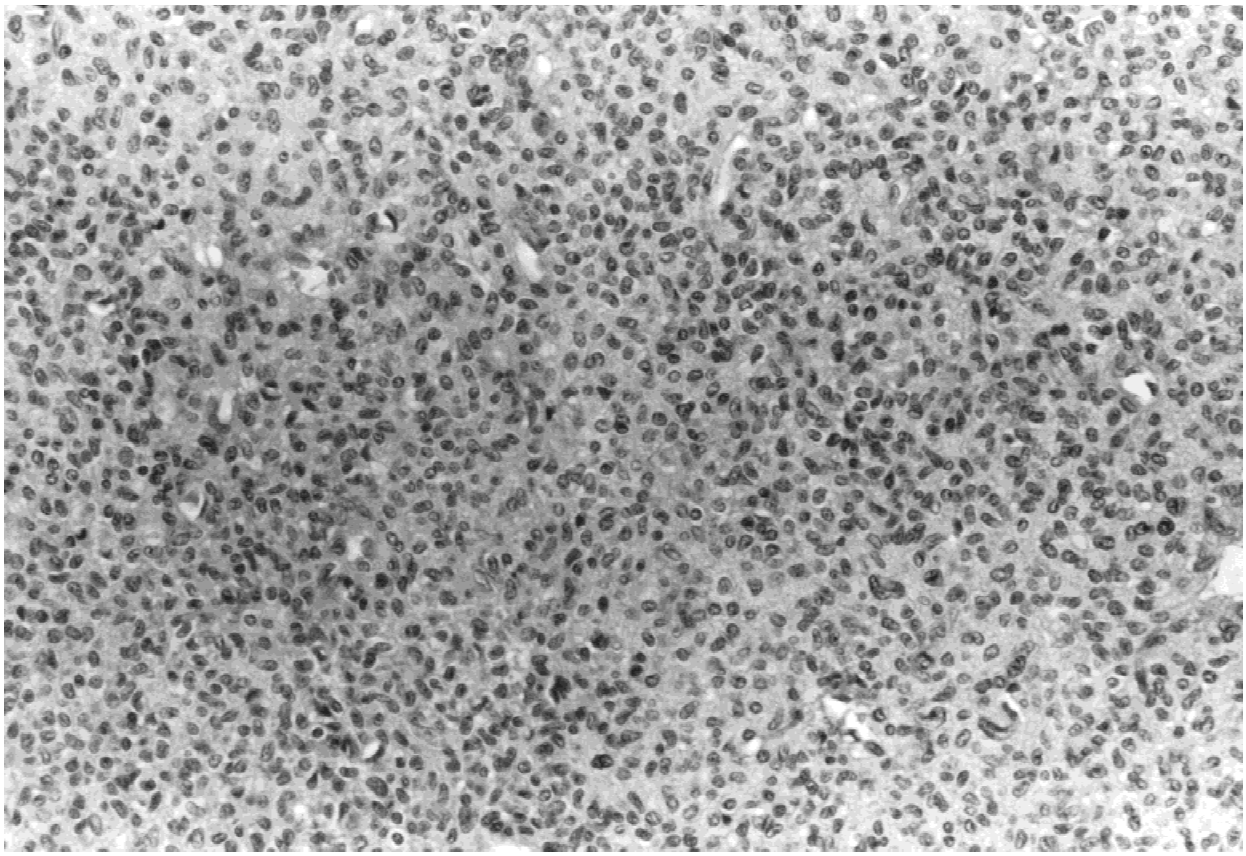

Fig. 6. At high power (magnification: 200×), the undifferentiated, hypercellular component demonstrates relatively uniform ovoid nuclei without mitotic figures, pleomorphism, or prominent nucleoli.

plete radiographic healing of his bone lesions was documented 6 months postoperatively, and the lower extremity pain and weakness resolved completely (Fig. 7). The rapid healing of the insufficiency fractures of osteomalacia suggests correction of the underlying pathologic process by tumor removal. A magnetic resonance imaging examination of the upper abdomen performed in November 1994 revealed no evidence of recurrent tumor.

Fig. 7. The Looser zones in the right femoral neck and fibula are completely healed 6 months following resection of the tumor.

DISCUSSION

Prader et al. [3] reported in 1959 the first case of tumor-associated osteomalacia that was successfully treated by resection of a giant-cell granuloma in a rib. A total of 79 cases of oncogenic rickets or osteomalacia have been reported in the literature. Most commonly, the tumors are of vascular, mesenchymal, or fibrous origin [3,4]. Although the majority of cases are associated with malignancies, the syndrome has also been reported in association with benign lesions such as hemangioma, giant-cell tumor, pigmented villonodular synovitis, and nonossifying fibroma [5]. This case represents only the second report of a mesenchymal chondrosarcoma causing oncogenic osteomalacia [6].

Huvos et al. [7] treated and followed 32 patients with mesenchymal chondrosarcoma. Their treatment included radiation, surgical resection, and chemotherapy (Ewing protocol). Their 10-year survival rate was 28%. These patients' clinical courses were characterized by local recurrence preceding metastasis. There were 10 pulmonary, 16 nodal, and 4 osseous metastases.

Oncogenic osteomalacia typically presents with complaints of weakness and the gradual onset of pain in weight-bearing areas (legs, ankles, and hips). Osteomalacia is usually confirmed by radiographic signs or bone

biopsy [5]. The tumor is usually identified after the onset of complaints. Characteristically, the biochemical findings consist of hypophosphatemia, increased urinary phosphate excretion, increased alkaline phosphatase, and normal calcium levels [6]. Low serum levels of 1.25 dihydroxyvitamin D have also been reported [5,8]. Musculoskeletal symptoms and radiographic changes generally resolve rapidly after tumor removal. Restoration of normal serum levels of dihydroxyvitamin D and phosphorus have been reported as rapidly as 16 and 28 hr, respectively, after resection of a mesenchymal tumor from the sole of the foot [9]. Failure of symptoms to resolve should suggest incomplete resection or possible recurrence of the primary tumor [5].

Oncogenic osteomalacia secondary to mesenchymal chondrosarcoma has been previously reported by Stone et al. [6]. Their patient presented with complaints of pain and weakness in his legs, feet, ankles, and hips. He was initially diagnosed with phosphaturic osteomalacia, until a cyst-like growth was noted on his foot 8 months later. The tumor was resected and demonstrated to be mesenchymal chondrosarcoma. After resection, their patient improved as evidenced by laboratory values and repeat bone biopsy, without further treatment.

The etiology of tumor-induced osteomalacia has yet to be determined. It has been suggested that certain mesenchymal tumors elaborate a humoral factor that decreases the normal renal tubular reabsorption of phosphate, resulting in phosphate diabetes. Further research suggests that these humoral factors may work through parathyroid hormone receptors similar to parathyroid hormone-related peptide (PTHrP) in the hypercalcemia of malignancy. More recently, studies have focused on the similarities of possible factors associated with oncogenic osteomalacia and X-linked hypophosphatemic rickets [10].

Oncogenic osteomalacia is an unusual clinical entity characterized by its rarity and often by the late diagnosis of the offending primary tumor. The radiographic findings of osteomalacia typically resolve soon after tumor resection. In the case presented, a potentially worrisome lesion in the femoral neck resolved rapidly with expectant treatment following excision of a chest wall mass and phosphate supplementation.

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